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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 09/322,875 | 05/28/99 | CHUNTHARAPAI A | 11669.19US03 |

HM12/0328

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| EXAMINER | |
|---|---|
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| **ART UNIT** | **PAPER NUMBER** |
| 1644 | 16 |

**DATE MAILED:** 03/28/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/322,875 | Chuntharapai et al |
| **Examiner** | **Group Art Unit** |
| F. Pierre VanderVegt | 1644 |

☒ Responsive to communication(s) filed on *Jan 5, 2001* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), ~~or thirty days, whichever is longer~~, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

## Disposition of Claim

☒ Claim(s) *1-21, 23, 24, and 33-55* is/~~are~~ pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-21, 23, 24, and 33-55* is/~~are~~ rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

## Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

## Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4, 11, 15*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

## DETAILED ACTION

This application is a continuation-in-part of application serial number 09/237,299, which claims priority to provisional application 60/072,481.

Applicant should amend the specification at page 1 to reflect the priority information as well as the status of the parent application(s).

Claims 22 and 25-32 have been canceled without prejudice or disclaimer as being drawn to a non-elected invention.

New claims 33-55 have been added.

Claims 1-21, 23, 24 and 33-55 are currently pending in this application.

### *Election/Restriction*

1. Applicant's election without traverse of Group I, claims 1-21 and 23-24, in Paper No. 13, filed January 5, 2001, is acknowledged.

Newly submitted claims 33-55 are drawn to the same invention as elected claims 1-21 and 23-24 and will be examined in this Office Action.

### *Inventorship*

2. In view of the papers filed January 9, 2001, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by adding Avi Ashkenazi as a co-inventor with Anan Chuntharapai and Kyung Jin Kim.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

***Claim Rejections - 35 U.S.C. § 112***

3. Claims 11-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The hybridoma cell lines recited are essential to the invention claimed in claims 11-18. The reproduction of an identical cell line is an extremely unpredictable event. The cell line must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. It is noted that the cell lines have been deposited with ATCC. The specification disclosure on page 35, line 23 to page 36, line 14 indicates that the deposits were made under the Budapest Treaty. The specification indicates that the cell lines will be maintained for 30 years from deposit and that the public will have "unrestricted" access upon issuance or laying open. However, the specification also indicates that this availability is subject to an agreement between the assignee and the depository.

In order to fully satisfy the deposit requirements, an affidavit or declaration by Applicants, assignees or a statement by an attorney of record over his or her signature and registration number stating that the deposit has been made under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposit will be **irrevocably removed** upon the grant of a patent on this application and that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample or for the enforceable life of the patent, **whichever is longer** is required.

4. Claim 19 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the DNA encoding for the monoclonal anti-DR4 antibodies produced by the instantly disclosed hybridomas, does not reasonably provide enablement for DNA encoding for anti-DR4 antibodies in general. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Base claim 1 is drawn to any antibody which binds to DR4, provided said DR4 contains the recited polypeptide subsequence. Claim 19 is drawn to the DNA encoding the antibody of claim 1. While it may be routine in the art to sequence the coding sequence for a particular monoclonal antibody, the specification does not provide sufficient guidance for one in the art to determine the sequence of all anti-DR4 antibodies. Given the well known polymorphism of immunoglobulins / antibodies; it would have been undue experimentation to derive the vast repertoire of nucleic acids resulting from somatic recombination and hypermutation mutation encoding nucleic acids encoding DR4-specific antibodies. Further, the scope of the claim encompasses serum antibodies for whom DNA sequence information is unavailable, as the DNA encoding the antibody is not isolated with it. Without sufficient guidance and given the well known polymorphism of immunoglobulins / antibodies; it would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue to determine the vast repertoire of nucleic acids encoding DR4-specific antibodies. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

The specification does not describe nor enable nucleic acids encoding DR4-specific antibodies, commensurate in scope with the claimed invention.

5. Claims 19, 35, 44 and 49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 35, 44 and 49 are drawn to human antibodies which bind DR4 and cause apoptosis in at least one type of mammalian cancer cell. Claim 19 is drawn to the DNA encoding any anti-DR4 antibody. *Vas-Cath Inc. v. Mahurkar* ((CAFC, 1991) 19 USPQ2d 1111), clearly states that "Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See *Vas-Cath* at page 1117). The specification

does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). It is respectfully submitted that the instant specification, in fact, clearly teaches only the possession of murine antibodies to DR4 or murine monoclonal antibodies which have been made chimeric or humanized.

Accordingly, there is evidence that the full scope of the claimed invention was not in Applicant's possession as of the filing date sought.

Therefore, while the recitation of anti-DR4 antibodies in general, as well as engineered antibodies comprising human immunoglobulin sequence, is supported by the instant specification, the particular recitation of human antibodies to DR4 does not meet the written description provision of 35 USC 112, first paragraph.

Further, as stated supra, the nucleic acid structure of the DR4-specific antibodies encompassed by the claimed invention of claim 19 would have been expected to vary and the skilled artisan would not have able to predict the structure, given the nature of high polymorphism in immunoglobulin structure. Therefore, the skilled artisan would not have envisioned the detailed structure of the encompassed nucleic acids and conception has not been achieved, regardless of the complexity or simplicity of the method of isolation.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see *Vas-Cath* at page 1115).

***Claim Rejections - 35 U.S.C. § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-5, 9, 10, 20, 21, 23, 24, 33, 34, 38-40, 42, 43, 47, 48 and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pan et al (56 on form PTO-1449 filed 2/10/00) in view of Campbell (U on form PTO-892).

Pan et al teaches a receptor for the apoptosis-inducing peptide TRAIL. The receptor taught by Pan et al is known as "death receptor 4" or DR4 and is the same protein which is the target of the instantly claimed antibodies, as evidenced by the disclosure in the instant specification at page 5, lines 13-27 for example. Base claim 1 recites "comprising amino acid residues 24-218." Applicant is reminded that the term "comprising" is open-ended and therefore would open up the amino acid sequence to include other residues up to and including the entire DR4 protein. Pan et al does not teach anti-DR4 antibodies. Campbell teaches that "[i]t is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)" (page 29, section "Basic research" in particular). It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to make antibodies specific for the TRAIL receptor taught by Pan et al. One would have been motivated, with a reasonable expectation of success, to generate mAbs to the protein based on the fact that it is a conventional practice in the art to do so for further study, characterization and identification of a specific peptide.

7. Claims 1-10, 20, 21, 23, 24, 33, 34, 36-43, 45-48 and 50-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pan et al (56 on form PTO-1449 filed 2/10/00) in view of Campbell (U on form PTO-892) and Güssow et al (V).

The Pan et al and Campbell references have been discussed supra. The combined references do not teach humanized antibodies. Güssow et al teaches a method for humanizing mouse mAbs in which the CDRs of the mouse mAb are inserted into the framework regions of a

human antibody (see entire document). The method of Güssow et al comprises the amplification by PCR and cloning of the murine V genes (pages 105-114 in particular), oligonucleotide-directed mutagenesis to combine the murine CDRs with the human framework regions (pages 114-119 in particular) and insertion of the light and heavy chain constructs into separate expression vectors mating them with human Ig light or heavy chain constant region genes further comprising methotrexate and G418 markers (page 120 in particular). Güssow et al also teaches that humanization of mouse mAbs specific for an antigen is desirable for in vivo use in a human in order to avoid the generation of a HAMA response (first two paragraphs of document in particular). Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of humanized antibody teachings of Güssow et al to the teachings of Pan et al and Campbell to obtain a humanized anti-DR4 antibody. A person of ordinary skill in the art would have been motivated to have such products to produce a humanized antibody because the potential for generating a HAMA response exists and would increase during the course of an extended treatment or tracing/diagnostic regimen. One could have combined these references with a reasonable expectation of success based on the teaching of Güssow et al that "[u]sing the reshaping scheme described here we estimate the success rate for humanizing any particular monoclonal antibody to be approximately 80%" (page 120, last sentence in particular, emphasis added).

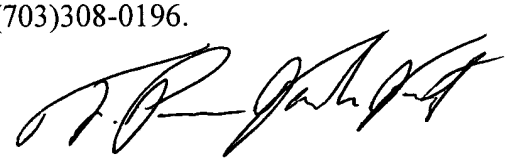
***Conclusion***

8. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

9. Papers related to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. Papers should be faxed to Group 1640 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The fax phone number for official documents to be entered into the record for Art Unit 1644 is (703)305-3014.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to F. Pierre VanderVegt, whose telephone number is (703)305-6997. The Examiner can normally be reached Tuesday through Friday and odd-numbered Mondays (on year 2001 365-day calender) from 6:30 am to 4:00 pm ET. A message may be left on the Examiner's voice mail service. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Christina Chan can be reached at (703)308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist, whose telephone number is (703)308-0196.

F. Pierre VanderVegt, Ph.D.
Patent Examiner
Technology Center 1600
March 26, 2001



F. PIERRE VANDERVEGT
PATENT EXAMINER